



National Toxicology Program

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September 13, 2017

Dr. Tina Bahadori
Director, NCEA
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 8601P
Washington, DC 20460

Re: NTP Mode of Action Research Relevant to the Formaldehyde IRIS Assessment

Dear Dr. Bahadori:

In October 2015, the American Chemistry Council Formaldehyde Panel (the Panel) submitted a letter to the previous NCEA Director, Dr. Ken Olden, calling attention to formaldehyde research conducted by the National Toxicology Program (NTP) National Institute of Environmental Health Sciences (NIEHS) which was presented at the 2014 and 2015 Society of Toxicology (SOT) meetings. The NTP research explored a hypothesized mode of action for leukemia in humans using two genetically predisposed strains of mice exposed to formaldehyde and found that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia. In October 2016, we submitted a follow-up letter to EPA communicating our formal request to NTP to publish the research in a peer-reviewed scientific journal or, at a minimum, for NTP to issue a public technical report. I am pleased to report that in August 2017, the NTP released a research report titled: Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation,¹ which provides the full details of the research summarily presented at SOT.

The objective of the NTP study was to evaluate the potential role of the Trp53 gene in nasal carcinogenicity, leukemia or lymphohematopoietic cancer, and potentially other neoplasms in genetically susceptible mice. Male Trp53 haploinsufficient (Trp53⁺) mouse strains (B6.129-Trp53^{tm1}Brd and C3B6.129F1-Trp53^{tm1}Brd) were exposed via inhalation to 0 ppm, 7.5 ppm or 15 ppm formaldehyde for 8 weeks. Because evidence suggests a possible role of the Trp53 gene in formaldehyde-induced nasal squamous cell carcinomas, the authors hypothesized that formaldehyde-induced loss of Trp53 would result in an increase in susceptibility to formaldehyde-induced nasal squamous cell carcinoma, and possibly leukemia and other neoplasms. However, the study found that inhalation of a maximum tolerated dose of formaldehyde did not cause nasal tumors, an increased prevalence of leukemia or lymphohematopoietic cancer, or any other type of cancer in Trp53⁺ mice. The results from this study increase the weight of evidence that formaldehyde exposure is not causally associated with leukemia. EPA's IRIS Stopping Rules² allow for the inclusion of new research information until a few months before an assessment is released for review. This study report provides important information related to postulated modes of action for formaldehyde and should be evaluated and integrated into the formaldehyde weight of evidence framework. We also strongly encourage EPA to reach out to the NTP for additional insight and information on this study.

¹ NTP Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation Research Report 3, National Toxicology Program, August 2017. The full report can be found at: https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/formaldehyde_508.pdf

² EPA IRIS Stopping Rules - https://www.epa.gov/sites/production/files/2014-06/documents/iris_stoppingrules.pdf



September 13, 2017

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EPA has previously indicated that it is committed to ensuring that the revised draft formaldehyde assessment reflects a transparent, rigorous, systematic review of available formaldehyde evidence which is consistent with the 2011 National Academy of Sciences (NAS) recommendations. The Panel has been committed to conducting research to address the recommendations of the NAS and engaging scientists on approaches to integrate the scientific evidence for formaldehyde. As we have previously communicated to EPA, in support of efforts to engage scientific experts on the formaldehyde science and methodologies for integrating the evidence, an invited scientific expert workshop has been scheduled for October 2017. This workshop will provide valuable insight on integrating the formaldehyde science which can inform the EPA's formaldehyde IRIS assessment. We are pleased that EPA IRIS staff accepted an invitation to participate in this workshop and look forward to the discussion.

The methods and approaches that EPA utilizes to systematically review and integrate the science to draw conclusions regarding potential human health risk will be a cornerstone in any future formaldehyde assessment. To help improve our understanding of the processes that will be applied to the formaldehyde assessment, we request that you provide responses to the following questions.

1. How is EPA considering new scientific information, like the NTP study, for incorporation into the weight of evidence for the formaldehyde IRIS assessment?
2. When did EPA last conduct a search of the formaldehyde literature for science to incorporate into the IRIS assessment and how frequently does EPA monitor the formaldehyde literature to identify potential studies that should be incorporated into the assessment?
3. What guidance documents or procedures will EPA utilize to evaluate study quality for studies relied upon to reach conclusions in the formaldehyde IRIS assessment? Please provide specific references if available.
4. When will EPA release a weight of evidence framework illustrating how various data streams (i.e. mechanistic, toxicology and epidemiology studies) are evaluated for quality and then integrated to reach conclusions about formaldehyde?
5. How has EPA addressed all the 2011 NAS recommendations for formaldehyde?
6. How will EPA seek public input and peer review on the formaldehyde IRIS assessment and what types of public meetings or workshops will be held to receive input?

Feel free to contact me by phone (202-249-6707) or email (Kimberly.White@americanchemistry.com) with any questions related to this letter. Additionally, a full copy of the study report is attached for your reference.

Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel

Cc:
Robert Kavlock
Dan Morgan
Kris Thayer
Richard Yamada

Attachment 1 – NTP Research Report on Absences of Formaldehyde-Induced Neoplasia in TRP53 Haploinsufficient Mice Exposed by Inhalation, August 2017



Message

From: White, Kimberly [Kimberly_White@americanchemistry.com]
Sent: 3/7/2017 1:16:09 PM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]
CC: Kavlock, Robert [Kavlock.Robert@epa.gov]
Subject: Letter Submitted on Behalf of the ACC Formaldehyde Panel
Attachments: Letter to EPA NCEA Director on Formaldehyde IRIS - Final- 03 07 17.pdf

Dear Dr. Bahadori:

Please find attached a letter submitted on behalf of the American Chemistry Council Formaldehyde Panel.

Kind Regards,

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March 7, 2017

Dr. Tina Bahadori
Director, National Center for Environmental Assessment
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Washington, DC 20460

Dear Dr. Bahadori:

Thank you for meeting with members of the American Chemistry Council (ACC) Formaldehyde Panel on February 21, 2017 to discuss the EPA's Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde (the "formaldehyde IRIS assessment"). As we discussed, formaldehyde is one of the most studied industrial chemicals in the world. Numerous epidemiology, toxicology, and mechanistic studies have been conducted which improve current understanding of the potential health effects associated with this chemical. These studies have also evaluated both endogenous formaldehyde and the potential contribution of exogenous exposure. After years of study, and hundreds of published scientific papers, recent science continues to strengthen the evidence that formaldehyde is a threshold nasal carcinogen and unlikely to be causally associated with other types of cancers in humans, particularly acute myeloid leukemia (AML).

In contrast to the body of scientific evidence, the EPA's 2010 draft formaldehyde IRIS assessment stated, "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, myeloid leukemia and lymphohematopoietic (LHP) cancers as a group." A 2011 National Academy of Sciences (NAS) peer review was highly critical of EPA's draft formaldehyde IRIS assessment concluding that EPA's assertion that formaldehyde causes leukemia, myeloid leukemia or related hematopoietic cancers was not supported in the draft assessment. Specifically, the NAS committee noted that EPA's conclusion that a causal relationship is supported by the data appeared to be subjective in nature, that no clear scientific framework had been applied by EPA in reaching that conclusion, and further noted inconsistencies in the epidemiologic data, weak animal data and the lack of mechanistic evidence.

In the six years since the NAS report was released, significant new peer reviewed science has been published that further calls into question any causal association between formaldehyde exposure and AML or other lymphohematopoietic malignancies. We consider these studies to be "game-changing" (*i.e.*, critical to the revised formaldehyde IRIS assessment) and they must be reviewed for pertinence and impact on the assessment's conclusions. These studies are summarized in Attachment A, and a few of the studies are also highlighted below:

- A 2015 scientific publication re-examined the underlying data from a seminal epidemiology study that EPA relied on in 2010 and concluded that the underlying data did not demonstrate a statistically significant association between formaldehyde and AML. (Checkoway *et al.*, 2015)



- Recent scientific publications re-evaluated the raw data from the study that was critical in establishing a possible mode of action for leukemia. The results indicated significant methodological limitations (including a failure by the authors to follow the reported protocol), as well as a lack of association between formaldehyde exposure and aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. (Gentry *et al.*, 2014, Albertini *et al.*, 2016 and Mundt *et al.*, 2017)
- Additional epidemiology studies included a follow-up of a large cohort of British industrial workers exposed to formaldehyde that concluded, “Our results provide no support for an increased hazard of myeloid leukemia, nasopharyngeal carcinoma, or other upper airway tumors from formaldehyde exposure.” (Coggon *et al.*, 2014)
- A series of published, peer reviewed studies demonstrated conclusively that environmental (or exogenous) formaldehyde that is inhaled or ingested does not reach the bone marrow (where transformations giving rise to leukemia occur). These studies clearly call into question the biological plausibility of a causal connection between exogenous formaldehyde exposure and leukemia. (Lai *et al.*, 2016, Yu *et al.*, 2015, Edrissi *et al.*, 2013, Moeller *et al.*, 2011)
- Two studies conducted by NIH using mice genetically predisposed to leukemias reported no association between formaldehyde exposure and leukemia or endpoints associated with leukemia. (Morgan *et al.*, 2015 and Morgan *et al.*, 2014)

Despite your assurances during the February 21st meeting that the formaldehyde IRIS assessment has been substantially revised to incorporate new scientific evidence generated since 2010 and that all of the NAS recommendations have been addressed and incorporated, we remain concerned that the revised formaldehyde IRIS assessment might not achieve an acceptable level of scientific rigor. We were surprised to learn that the stopping rule for the formaldehyde IRIS assessment already has been invoked at an unspecified date and without due notice to the public. We are disappointed in the continued lack of transparency by the Agency on how and when the stopping rules are applied and the Agency’s lack of commitment to using a weight of evidence approach for chemical assessments. As such, ongoing research and research currently undergoing peer review may be arbitrarily and inappropriately excluded from the assessment.

Specifically, the Formaldehyde Panel is concerned that: (a) a transparent, rigorous weight of evidence approach has not been developed or utilized in the formaldehyde IRIS assessment as called for by NAS; (b) programmatic improvements to be adopted for hazard identification and dose-response assessment have not been applied to the formaldehyde IRIS assessment; and (c) the “stopping rules” for formaldehyde have been invoked, without any communication to the public, and that this will preclude the consideration of important new science.

We believe that a revised formaldehyde IRIS assessment that fails to reflect a transparent weight of evidence assessment that fully and critically evaluates and integrates evidence from studies published since the release of the 2010 draft assessment, will not be scientifically robust and may include erroneous conclusions. As the NAS recommended in 2011, a systematic review of all of the studies is needed to support a weight of evidence approach, clearly identifying the highest quality studies and their role in drawing conclusions regarding the causal associations between formaldehyde exposure and health effects. This type of review is necessary to provide transparency surrounding the criteria that have been used to weigh evidence and assess causality in the formaldehyde IRIS assessment. Given that it has been six years since the NAS provided its recommendations, there is no compelling reason why programmatic improvements in systematic



Dr. Tina Bahadori

March 7, 2017

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review processes cannot also be adopted for formaldehyde. As such, we encourage you to perform a critical systematic review of all the data included in the formaldehyde IRIS assessment, including the research in Attachment A, before any revised formaldehyde IRIS assessment undergoes external review. The new science summarized in Attachment A rises to the level of “game changing” findings and their inclusion and integration into your review is essential.

We trust that as the new EPA NCEA Director you are committed to ensuring that the revised formaldehyde IRIS assessment fully addresses the scientific recommendations identified by the NAS in 2011, both process related and specific to formaldehyde, considering the best available formaldehyde science generated to address those NAS recommendations and integrating all streams of the scientific evidence to reach conclusions regarding formaldehyde’s carcinogenicity and toxicity. We hope you will fully consider and address the concerns raised in this letter prior to the release of a revised draft formaldehyde IRIS assessment for public comment and we look forward to opportunities to work constructively with the EPA moving forward.

Sincerely,

Kimberly Wise White, PhD

Senior Director

American Chemistry Council (ACC)

Chemical Products & Technology Division

Cc:

Robert Kavlock



ATTACHMENT A
SUMMARY OF FORMALDEHYDE SCIENCE ADDRESSING NAS RECOMMENDATIONS



NAS (2011) Comment/ Data Gap	New Evidence
Epidemiological Evidence	
<p>Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (p. 113)</p>	<p>Conducted additional and refined analysis on the key underlying data (including specifically exposure information which had not been previously provided) utilized in a study relied upon in the draft IRIS assessment (e.g. Zhang <i>et al.</i>, 2010). Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Additionally, among formaldehyde-exposed workers, no association was observed between individual formaldehyde exposure estimates and frequency of aneuploidy, which the original study authors suggested were indicators of myeloid leukemia risk. <i>Mundt et al.</i>, (2017))</p> <p>New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. <i>Checkoway et al.</i>, (2015)</p> <p>Associations seen between formaldehyde exposure and Hodgkin leukemia and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. <i>Checkoway et al.</i>, (2015)</p>
<p>Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (p. 113)</p>	<p>A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoietic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation. <i>Checkoway et al.</i>, (2012)</p>



<p>Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (pp. 112-113)</p>	<p>Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure.</p> <p>Few deaths occurred within 20+ years of last peak exposure.</p> <p>Hodgkin lymphoma relative risk estimates suggested trends for both cumulative ($P_{trend}=0.05$) and peak ($P_{trend}=0.003$) exposures.</p> <p>Suggestive associations with peak exposure observed for chronic myeloid leukemia, based on very small numbers. Due to the lack of concordance with other epidemiologic studies and lack of a plausible biological mechanism, the authors considered any causal interpretations of the observed risk patterns to be at most tentative.</p> <p>No other lymphohematopoietic malignancy was associated with either chronic or peak exposure. <i>Checkoway et al., (2015)</i></p>
<p>The selection and use of the NCI cohort (Beane-Freeman et al. 2009) should be further justified. (p. 112)</p>	<p>Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941-2012. Results provided no support for an increased hazard of myeloid leukemia from formaldehyde exposure. <i>Coggon et al., (2014)</i></p> <p>Analyzed 15,332 newly diagnosed cases of AML (i.e., not deaths) diagnosed from 1961 to 2005 in Finland, Norway, Sweden, and Iceland, and 76,660 matched controls. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde. <i>Talibov et al., (2014)</i></p> <p>Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. <i>Meyers et al., (2013)</i></p> <p>Studied occupational risk factors among 671 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy. No increased risk of AML was associated with low exposure to formaldehyde (HR 1.01, 95% CI 0.65 - 1.57) and no AML cases occurred among individuals in the high formaldehyde exposure category. <i>Saberi et al., (2013)</i></p>



Toxicological Evidence	
Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (p. 110)	<p>No cases of leukemia or lymphohematopoietic neoplasia were seen. Formaldehyde inhalation did not cause leukemia in genetically predisposed C3B6.129F1-<i>Trp53</i>^{tm1Brd} mice. <i>Morgan et al., (2014)</i></p> <p>Formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. <i>Morgan et al., (2015)</i></p>
Mode of Action Evidence	
Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (p. 58)	<p>Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. <i>Schroeter et al., (2014)</i></p> <p>With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. <i>Yu et al., (2015)</i></p>
Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (p. 5)	<p>Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. <i>Yu et al., (2015); Edrissi et al., (2013); Lu et al., (2012); Moeller et al., (2011); Lu et al., (2011)</i></p>



<p>Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (p. 5)</p>	<p>Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to formaldehyde alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow.</p> <p>Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species– a probable prerequisite for leukemogenesis. <i>Albertini et al., (2016)</i></p> <p>Reanalysis of selected raw data from the Zhang et al. (2010) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010) raise sufficient questions that limit the use of Zhang et al. (2010) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. <i>Gentry et al., (2013); Mundt et al., (2017, in press)</i></p>
<p>Dose-Response Assessment</p>	
<p>Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (p. 14)</p>	<p>The documentation of the methods applied in the USEPA (2010) IRIS document lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from Beane Freeman et al., (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. <i>Van Landingham et al., (2016)</i></p>
<p>BBDR models developed by Conolly and co-workers should be used. (p. 58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (p. 57)</p>	<p>Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand if exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. <i>Clewell et al., (in preparation)</i></p>
<p>Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (p. 14)</p>	<p>Results of the “Bottom-up “ approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. <i>Starr and Swenberg, (2013)</i></p>



	Updated “Bottom-Up” risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers. <i>Starr and Swenberg (2016)</i>
Methods for Evidence Integration	
EPA’s approach to weight of evidence should include “a single integrative step after assessing all of the individual lines of evidence”. Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (p. 113)	A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode of action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. <i>Rhomberg et al., (2011); Rhomberg et al., (2015), Swenberg et al.,(2013)</i>

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Message

From: Thayer, Kris [thayer.kris@epa.gov]
Sent: 9/22/2017 8:55:07 AM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]
Subject: RE: Formaldehyde Science Invited Expert Workshop
Attachments: 1 - Attendee List.pdf; 3 - Charge Questions.pdf; 2 - Agenda.pdf

I see I'm listed as helping address this charge question. Hmmm. I guess okay if I keep it basic and not LHP focused?

What methods for assessing causality and evidence integration are best applied to the available data for LHP cancer for conducting a hazard assessment (e.g., Bradford Hill criteria, biological systems approach, hypothesis based weight of evidence framework, systematic review, combination of approaches?)

Suggested Discussants for Charge Question: Mel Andersen, Paulo Boffetta, Harvey Checkoway, David Coggon, Ken Mundt, , Enrico Pira, Kris Thayer

From: Bahadori, Tina
Sent: Thursday, September 21, 2017 11:09 PM
To: Thayer, Kris <thayer.kris@epa.gov>
Subject: RE: Formaldehyde Science Invited Expert Workshop

Maybe we can share the agenda and attendee list with Richard, Bob, et al on Monday.
T.

From: Thayer, Kris
Sent: Wednesday, September 20, 2017 11:38 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>
Subject: FW: Formaldehyde Science Invited Expert Workshop

See link for materials

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]
Sent: Wednesday, September 20, 2017 11:01 AM
Cc: Swenberg, James A <jswenber@email.unc.edu>; mundt@email.unc.edu; Hartwell, Hadley J <hadley_hartwell@med.unc.edu>
Subject: Re: Formaldehyde Science Invited Expert Workshop

Dear Formaldehyde Science Invited Expert Workshop Participants;

Thank you for your interest in participating in the Invited Expert Workshop to explore the latest science on formaldehyde carcinogenicity being held October 10 -11, 2017 at the UNC Friday Center located at 100 Friday Center Drive, Chapel Hill, NC 27599. The Workshop will be co-chaired by Dr. Jim Swenberg and Dr. Ken Mundt and the Workshop discussion will focus on ((1) review the evidence of causal relationships between formaldehyde exposure and cancer; (2) discuss the role of integrating available scientific data to reach conclusions regarding carcinogenicity; (3) identify data requirements and gaps regarding cancer hazard and risk assessment, and (4) identify key endpoints, data, and preferred formats for developing objective and transparent risk assessments. The authors of many relevant studies of formaldehyde and cancer risk have been invited to participate in this Workshop as well as senior scientists with expertise in hazard assessment, mode of action analysis, integration of evidence and quantitative risk assessment.

In preparation for the Workshop, please review the following additional relevant information:

1. Workshop Materials - A link has been provided here <https://acc.ftpstream.com/38419/091e9d5010d144889dd9e4a5ee4cebd5/Formaldehyde%2bWorkshop%2bMaterials.zip> where you can download all the meeting materials, which include:
 - Tentative Workshop Agenda
 - Participants List
 - Charge Questions
 - Suggested Reading List

The Workshop agenda includes a considerable allotment of time for participant discussion on the charge questions. Every attendee is encouraged to review the charge questions and actively provide input during the workshop discussion. In the charge questions document, a proposed list of participants has been identified related to each charge question based on area of expertise but all participants should feel free to provide input on any charge question. While not required, if participants wish to prepare 1-2 slides to highlight a topic are presented in the charge questions feel free to do so.
2. Travel Reimbursements - For those receiving travel reimbursements, please be sure to return all completed forms to Ms. Hadley Hartwell at the University of North Carolina (email: hadley_hartwell@med.unc.edu) as soon as possible. If you have questions regarding any of the required forms please contact Ms. Hartwell directly.
3. October 10th Dinner - For those available, the workshop organizers will host a participants dinner at 6:30pm. If you are planning to attend please RSVP to Kimberly White (email: Kimberly_White@americanchemistry.com) by September 30th.

We look forward to your participation in the workshop and please do hesitate to contact me, Ms. Hartwell or the workshop chairs with any questions.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division
Kimberly_White@americanchemistry.com
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Formaldehyde Science Invited Experts Workshop Attendee List

Invited and Confirmed Participants	
Name	Affiliation
Barbara Bankoff	Consultant to Koch Industries, Inc.
Chap Thompson	ToxStrategies, Inc.
David Coggon	University of Southampton
David Dunlap	Koch Industries, Inc.
Enrico Pira	University of Turin
Gary Marsh	University of Pittsburg
Harvey Checkoway	University of California San Diego
Harvey Clewell	ScitoVation/
Heinz-Peter Gelbke	Consultant to Formacare
Helmut Greim	Independent Scientist
Hermann Bolt	Independent Scientist
Jim Bus	Exponent
Jim Sherman	Celanese
Jim Swenberg	University of North Carolina
Joseph "Kip" Haney	Texas Commission of Environmental Quality
Kenneth Mundt	Ramboll Environ
Kimberly White	American Chemistry Council
Kris Thayer	Environmental Protection Agency
Mark Gruenwald	Hexion
Melvin Andersen	ScitoVation
Michael Thirman	University of Chicago
Paolo (Paul) Boffetta	Icahn School of Medicine at Mount Sinai
Raj Sharma	Georgia-Pacific
Robinan Gentry	Ramboll Environ
Rory Conolly	Environmental Protection Agency
Sam Cohen	University of Nebraska Medical Center
Stewart Holm	American Forest & Paper Association
Tom Starr	TBS Associates
Invited and Unconfirmed Participants	
Name	Affiliation
Dan Morgan	National Institute of Environmental Health Sciences
Dick Albertini	University of Vermont
Joe Roderick	Ramboll Environ
KJ Patel	MRC Laboratory of Molecular Biology
Laura Beane-Freeman	National Cancer Institute
Louping Zhang	University of California Berkley
Rusty Thomas	Environmental Protection Agency
Sue MacMillan	Oregon Department of Environmental Quality

AGENDA

FORMALDEHYDE SCIENCE INVITED EXPERTS WORKSHOP UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK – FROM DATA INTEGRATION TO RISK EVALUATION

October 10 – 11, 2017

Location: UNC Friday Center, 100 Friday Center Drive, Chapel Hill, NC 27599

TUESDAY, OCTOBER 10, 2017	
Time	Item
8:00am – 9:00am	BREAKFAST (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 9:00am	REGISTRATION (Outside of Conference Room: Tentatively Mountain Laurel)
9:00am -9:05am	Welcome and Logistics - Kimberly White and Jim Swenberg (5 minutes)
9:05am -9:10am	Workshop Purpose and Objectives - Ken Mundt (5 minutes)
9:10am -9:25am	Understanding the Formaldehyde Science and Putting the Puzzle Pieces Together – Integrating New Science into Risk Evaluation Processes - Robinan Gentry (15 minutes)
9:25am – 9:40am	Summary of Global Risk Assessment Approaches for the Formaldehyde Science - General Approaches in EU, Canada, WHO and the US - Jim Bus (15 minutes)
SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY (Chair: Helmet Greim)	
9:40am – 10:00am	European Approach for Evaluating the Formaldehyde Science: OEL, Nasal Impacts and Threshold Assessment - Hermann Bolt (20 minutes)
10:00am -10:20am	Formaldehyde and Nasal Carcinogenicity: What Does the Epidemiology and Animal Data Tell Us? - Gary Marsh (20 minutes)
10:20am – 12:00pm	Discussion – Key Views by Participants on Charge Questions and MOA Framework <ul style="list-style-type: none"> • Charge Question #1 Discussion (25 minutes) • Charge Question #2 Discussion (25 minutes) • Charge Question #3 Discussion (25 minutes) • Open Discussion (25 minutes)
12:00pm – 12:45pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Area)
SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY (Chair: Ken Mundt)	
12:45pm – 1:05pm	Key Events and Considerations for LHP Cancers - Ken Mundt (20 minutes)
1:05pm – 1:25pm	Overview: Epidemiology Evidence - Harvey Checkoway (20 minutes)
1:25pm – 1:45pm	Overview of the Animal Science - Chad Thompson (20 minutes)
1:45pm – 2:05pm	LHP Cancers and Biological Plausibility – Can Exogenous Formaldehyde Reach the Bone Marrow? Jim Swenberg (20 minutes)
2:05pm – 3:45pm	Discussion - Key Views by Participants on Charge Questions and MOA Framework <ul style="list-style-type: none"> • Charge Question #4 Discussion (25 minutes) • Charge Question #5 Discussion (25 minutes) • Charge Question #6 Discussion (25 minutes) • Open Discussion (25 minutes)
3:45pm – 4:00pm	BREAK (UNC Friday Center – Main Vestibule and Dining Area)
4:00pm – 4:15pm	Looking Across Data Streams to Draw Conclusions Regarding Causality: Key Considerations in the Formaldehyde Science Harvey Clewell (15 minutes)

AGENDA

4:15pm – 5:30pm	Discussion – Key Views by Participants on Charge Questions <ul style="list-style-type: none"> • Charge Question #7 Discussion (30 minutes) • Charge Question #8 Discussion (30 minutes) • Open Discussion (15 minutes)
5:30pm	ADJOURN DAY 1 OF WORKHOP
6:30pm – 8:00pm	DINNER – OFFSITE (Location: TBD)

WEDNESDAY, OCTOBER 11, 2017	
Time	Item
8:00am – 9:00am	BREAKFAST (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 9:00am	REGISTRATION (Outside of Conference Room: Tentatively Mountain Laurel)
SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION? (Chair: Jim Sherman)	
9:00am – 9:15am	Overview of State-of-the-Science Approaches for Data Integration - Kimberly White (15 minutes)
9:15– 9:30am	Recap of Day 1 Discussion: Identified Data Gaps and Uncertainties - Information Needs for a Formaldehyde Risk Evaluation Mel Andersen (15 minutes)
9:30am – 11:45am	Discussion – Key Views by Participants on Charge Questions <ul style="list-style-type: none"> • Charge Question #9 Discussion (20 minutes) • Charge Question #10 Discussion (30 minutes) • Charge Question #11 Discussion (30 minutes) • Charge Question #12 Discussion (20 minutes) • Charge Question #13 Discussion (20 minutes) • Open Discussion (15 minutes)
11:45am – 12:00pm	Workshop Wrap and Next Steps
12:00pm	LUNCH (UNC Friday Center – Main Vestibule and Dining Area)
1:00pm	ADJOURN DAY 2 OF WORKSHOP

CHARGE QUESTIONS

SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY

1. Does the available scientific evidence support a specific MOA and causal association with NPC?
 - What mechanistic evidence is available to support the proposed modes of action frameworks discussed for NPC? What are the uncertainties?

Suggested Discussants for Charge Question: Mel Andersen, Hermann Bolt , Harvey Clewell, Rory Conolly, Gary Marsh

2. What are the key animal data for characterizing the shape of the dose-response curve for formaldehyde-induced nasal tumors? What are the key epidemiological studies for formaldehyde-induced nasal tumors and how would you reconcile differences between those studies?
 - If a causal association can be established for human, what exposure metrics are associated with evidence of carcinogenicity? Is there evidence of a threshold for NPC in humans?

Suggested Discussants for Charge Question: Mel Andersen, Herman Bolt, Harvey Clewell, , Rory Conolly, Peter Gelbke, Helmut Greim, Gary Marsh

3. What quantitative methods (e.g., linear and non – linear low dose extrapolation, threshold, PBPK modeling for dose-response assessment) would best characterize the potential for NPC risk in humans?
 - Are there uncertainties with any of these quantitative methods that suggest this type of modeling should not be applied?

Suggested Discussants for Charge Question : Harvey Clewell, Rory Conolly, Robinan Gentry, Tom Starr

SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY

4. What does the totality of the animal and epidemiology evidence tell us about the potential for a causal association with LHP and what conclusions can be drawn?
 - What role does endogenous production play in drawing conclusions regarding LHP?
 - Do the available data support a specific mode of action for hematopoietic cancers?

Suggested Discussants for Charge Question: Paulo Bofetta, Harvey Checkoway, David Coggon, Sam Cohen, Robinan Gentry, Joseph Haney, Erico Pira, Jim Swenberg, Michael Thirman, Chad Thompson

5. What mechanistic data are critical to understanding a causal association between formaldehyde exposure and specific hematopoietic cancers?

Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg, Michael Thirman

CHARGE QUESTIONS

6. Do epidemiology studies provide useful dose-response data for LHP?
Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg, Michael Thirman
7. What methods for assessing causality and evidence integration are best applied to the available data for LHP cancer for conducting a hazard assessment (e.g., Bradford Hill criteria, biological systems approach, hypothesis based weight of evidence framework, systematic review, combination of approaches?)
Suggested Discussants for Charge Question: Mel Andersen, Paulo Boffetta, Harvey Checkoway, David Coggon, Ken Mundt, , Enrico Pira, Kris Thayer
8. What uncertainties are important for consideration when integrating the available evidence? **Suggested Discussants for Charge Question:** Mel Anderson, Jim Bus, Harvey Clewell, Sam Cohen, Robinan Gentry, Tom Starr

SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION?

9. What should be considered as the problem formulation and questions to be addressed when conducting a formaldehyde risk evaluation?
10. What are the best available approaches to conduct a robust evaluation of formaldehyde carcinogenic potential?
11. How can the approaches used to evaluate and integrate scientific evidence inform the risk assessment?
 - What aspects of the Biological Systems Approach can be used to integrate the formaldehyde data?
 - How can hypothesis based weight of evidence approach be to integrate the data streams for determination of causality?
12. What needs to be added or changed in the draft IPCS Mode of Action Framework nasal carcinogenicity?
13. What is the comparative weight of evidence for each hypothesized mode of action for nasal carcinogenicity?

Suggested Discussants for All Charge Questions – All Participants

Message

From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]
Sent: 1/16/2018 8:37:08 PM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]
Subject: Re: Meeting with ACC on Formaldehyde

Good

Sent from my iPad

On Jan 16, 2018, at 3:18 PM, Bahadori, Tina <Bahadori.Tina@epa.gov> wrote:

 OAR and OP are going to join this briefing.
 T.

-----Original Appointment-----

From: Gentry, Nathan **On Behalf Of** Orme-Zavaleta, Jennifer
Sent: Tuesday, January 16, 2018 11:23 AM
To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin; Bahadori, Tina
Cc: Vandenberg, John; Thayer, Kris; Lavoie, Emma; Axelrad, Daniel; Ross, Mary; Bussard, David
Subject: Meeting with ACC on Formaldehyde
When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 41213 RRB/via video to B249

From: White, Kimberly [mailto:Kimberly.White@americanchemistry.com]
Sent: Monday, December 04, 2017 8:22 AM
To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>
Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21st letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22nd to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

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Regul Toxicol Pharmacol. 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006.
[Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA¹, Gentry PR², Dell LD², Rodricks JV², Boffetta P³.

Author information

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehyde causes leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

KEYWORDS:

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

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Kind Regards,

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Senior Director, Chemical Products & Technology Division
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Message

From: Kuhn, Kevin [Kuhn.Kevin@epa.gov]
Sent: 1/24/2018 7:19:16 PM
To: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Rodan, Bruce [rodan.bruce@epa.gov]; Yamada, Richard (Yujiro) [yamada.richard@epa.gov]; Fleming, Megan [Fleming.Megan@epa.gov]; Christian, Megan [Christian.Megan@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]
CC: Vandenberg, John [Vandenberg.John@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Axelrad, Daniel [Axelrad.Daniel@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Mazza, Carl [Mazza.Carl@epa.gov]; Sasser, Erika [Sasser.Erika@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]
Subject: RE: Meeting with ACC on Formaldehyde
Attachments: background.pdf; formaldehyde ppt.pdf; one pager.pdf; paper.pdf

Hi All,

Please find attached the background documents under discussion.

Kevin Kuhn
ORD/EPA
(202) 564-4835
Mobile: (202) 309-3969

-----Original Appointment-----

From: Orme-Zavaleta, Jennifer
Sent: Monday, December 4, 2017 12:07 PM
To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin; Bahadori, Tina
Cc: Vandenberg, John; Thayer, Kris; Lavoie, Emma; Axelrad, Daniel; Ross, Mary; Bussard, David; Mazza, Carl; Sasser, Erika; Rimer, Kelly; Vasu, Amy; Kraft, Andrew; Glenn, Barbara
Subject: Meeting with ACC on Formaldehyde
When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 41213 RRB/via video to B249; call-in: 202-991-0477, code: 2997121

From: White, Kimberly [<mailto:Kimberly.White@americanchemistry.com>]
Sent: Monday, December 04, 2017 8:22 AM
To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>
Subject: Follow-up

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Regul Toxicol Pharmacol. 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA¹, Gentry PR², Dell LD², Rodricks JV², Boffetta P³.

Author information

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehyde causes leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

KEYWORDS:

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

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Kind Regards,

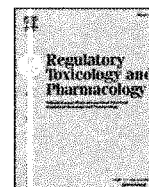
Kimberly Wise White, Ph.D. | American Chemistry Council
Senior Director, Chemical Products & Technology Division

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Commentary

Six years after the NRC review of EPA's *Draft IRIS Toxicological Review of Formaldehyde*: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

Kenneth A. Mundt^{a,*}, P. Robinan Gentry^a, Linda D. Dell^a, Joseph V. Rodricks^a, Paolo Boffetta^b

^a Environment and Health, Ramboll Environ, Amherst MA, United States

^b Icahn School of Medicine at Mount Sinai, New York, NY, USA

ARTICLE INFO

Keywords:

Regulatory science
Hazard evaluation
Evidence integration
Epidemiology
Toxicology
Mechanistic studies

ABSTRACT

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its *Draft IRIS Toxicological Review of Formaldehyde* (“Draft IRIS Assessment”), also concluding that formaldehyde causes leukemia. Peer review of the Draft IRIS Assessment by a National Academy of Science committee noted that “causal determinations are not supported by the narrative provided in the draft” (NRC 2011). They offered recommendations for improving the Draft IRIS assessment and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key recommendations made by NRC and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde’s commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

1. Introduction

Classification and regulation of human carcinogens is a key component to the protection and improvement of public health. However, proper regulation of industrial chemicals hinges on both valid hazard identification and quantitative risk assessment. Increasingly, hazard identification – at least where adequate scientific evidence is available – draws on critically assessing and integrating evidence across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization of exposure, which is complicated, especially where historical measures are sparse or do not exist. Where adequate evidence from some or all of these is lacking, and where important uncertainties remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence accumulates, more science-focused methods can be employed, reducing uncertainties, leading to sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as discussed in this commentary. Recent evaluations of formaldehyde, coupled with

improved critical review and evidence integration expectations and new, more focused scientific evaluations, illustrate the dynamic nature of scientific inquiry, the need for parallel refinement of hazard characterization, and subsequently, stronger risk assessment.

In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. The impetus for the new science summarized below is derived from the International Agency for Research on Cancer’s (IARC) 2009 classification of formaldehyde as a known cause of leukemia in Monograph 100F (Baan et al., 2009; IARC, 2012), the US Environmental Protection Agency’s (EPA’s) similar classification in the *Draft IRIS (Integrated Risk Information System) Toxicological Review of Formaldehyde – Inhalation Assessment* (hereafter referred to as “Draft IRIS Assessment”) (EPA, 2010), and the criticisms and recommendations presented in two National Academy of Science (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on the IRIS process itself (NRC, 2011; NRC, 2014a). Various organizations and agencies have contributed to or sponsored the new science, including governments and universities, as well as industry. In revising and finalizing the Draft IRIS

* Corresponding author.

E-mail address: kmundt@ramboll.com (K.A. Mundt).

<https://doi.org/10.1016/j.yrtph.2017.11.006>

Received 7 April 2017; Received in revised form 27 October 2017; Accepted 15 November 2017

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Table 1
Summary of major formaldehyde carcinogenicity classifications and noted scientific basis.

Year	Agency	Carcinogenicity Classification	Findings
1981	NTP (1981)	Anticipated to be a human carcinogen	Epidemiological evidence. Not discussed Toxicological evidence. One study cited (Svenberg et al., 1980). Nasal cancers: "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Svenberg et al., 1980)."
1981 ^a	IARC (1982a; b)	Possibly carcinogenic to humans (Group 2B)	Epidemiological evidence. Inadequate (6 epidemiology studies) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.
1982	NTP (1982)	Anticipated to be a human carcinogen	Epidemiological evidence. Inadequate (cites IARC, 1982a; b) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results. Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.
1987 ^b	IARC (1987)	Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports. Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies." Toxicological evidence. Sufficient No changes in information reported from IARC (1982b) Supporting data. "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl 6, 1987)."
1991	EPA (1991)	Probable human carcinogen (Group B1)	Epidemiological evidence. Limited (28 studies considered) Nasal cancers: "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7) Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8) Toxicological evidence. Sufficient, nasal squamous cell carcinomas Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies. Supporting data. "The classification is supported by <i>in vitro</i> genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde." (p. 7)
1994 ^c	IARC (1995)	Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses. Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or hematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p. 334) Toxicological evidence. Sufficient (nasal squamous cell carcinomas) Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation. Supporting data. Genotoxic in variety of experimental systems <i>in vivo</i> . Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells <i>in vitro</i> .

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2004 ^d	IARC (2006)	Carcinogenic to humans (Group 1)	<p>Epidemiological evidence. Sufficient, based on nasopharyngeal cancer Leukemia: "There is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276)</p> <p>Toxicological evidence. Sufficient (nasal squamous cell carcinoma)</p> <p>Supporting data. Mechanism for inducing myeloid leukemia is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells. "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans." (p. 280)</p>
2009 ^e	IARC (2012)	Carcinogenic to humans (Group 1)	<p>Epidemiological evidence. Formaldehyde causes cancer of the nasopharynx and leukemia.</p> <p>"The Working Group was not in full agreement on the evaluation of formaldehyde causing leukemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430)</p> <p>Toxicological evidence.</p> <p>"Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427) "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428) Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation.</p> <p>Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological precursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430)</p> <p>"Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430)</p>
2010	Draft IRIS Assessment (EPA, 2010)	Carcinogenic to humans	<p>Epidemiological evidence. Sufficient. "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (p. 6–46).</p> <p>All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (p. 4–180).</p> <p>All leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (p. 4–182)</p> <p>Myeloid leukemia: "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Pinkerton et al., 2003; Hayes et al., 1990; Stroup et al., 1986; Wabnitz and Fraumeni, 1984, 1983; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (p. 4–185)</p> <p>Toxicological evidence. Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde.</p> <p>"Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Columbus Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p. 6–21)</p> <p>Supporting data. "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been commented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p. 6–22)</p>

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2012	NTP (2011)	Known to be a human carcinogen	<p>Epidemiological evidence. Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia</p> <p>“Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia.” (p. 195)</p> <p>Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: “Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these tumors were exposure-related, because of limitations in the reporting of these tumors (Sofritti et al., 2002).” (p. 198)</p> <p>Supporting data. “Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves, 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al., 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2–3 µg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck et al., 1983; Casanova et al., 1988; Heck and Casanova, 2004). Moreover, N2-hydroxymethyl-dG-DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu et al., 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden et al., 2006; Pyatt et al., 2008). However, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse haematological effects in humans.” (p. 199)</p> <p>Epidemiological evidence. Limited</p> <p>“In conclusion, while some studies have found increased rates of leukemia, the epidemiology data do not show consistent findings across studies for leukemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukemia rates among embalmers, pathologists and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukemia.” (p.41)</p> <p>Toxicological evidence. “No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumors in inhalation study of rats and mice (Kerns et al., 1983).” (p.22)</p> <p>Supporting data. “Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the point of entry.” (p.44)</p>
2012	RAC (2012)	Carc. 1B - H50 ¹ May cause cancer	<p>Epidemiological evidence. Limited</p> <p>“In conclusion, while some studies have found increased rates of leukemia, the epidemiology data do not show consistent findings across studies for leukemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukemia rates among embalmers, pathologists and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukemia.” (p.41)</p> <p>Toxicological evidence. “No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumors in inhalation study of rats and mice (Kerns et al., 1983).” (p.22)</p> <p>Supporting data. “Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the point of entry.” (p.44)</p>

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2016	Scientific Committee on Occupational Exposure Limits for Formaldehyde (Bolt et al., 2016)	Carcinogen Group C (genotoxic carcinogen with a mode-of-action based threshold)	<p>Epidemiological evidence. Limited. Leukemias: "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45)</p> <p>Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49)</p> <p>Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)</p>

^a IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 vol of the IARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."

^b IARC Working Group met March 1987.

^c IARC Working Group met October 1994; monograph published 1995.

^d IARC Working Group met June 2004; monograph published 2006.

^e IARC Working Group met October 2009; monograph published 2012.

^f EU harmonized classification and labelling.

Assessment (EPA, 2010), EPA now has the opportunity to incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

2. Formaldehyde cancer hazard evaluation

The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s, including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA), and the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (Table 1). Except for the RAC review (RAC, 2012) and the SCOEL review (Bolt et al., 2016), which reclassified formaldehyde as a Carcinogen Category 1B (i.e., presumed to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with a mode of action based threshold), respectively, these reviews classified formaldehyde as a known human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA, 2010; IARC, 2012; NTP, 2011). Differences between NTP (2011) and EPA draft classifications (final version of the EPA review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC (2012) and the RAC (RAC, 2012) evaluations have been discussed by Marsh et al. (2014).

The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous production and high reactivity. This prompted closer scrutiny regarding the methods used to critically evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence across lines of inquiry such as animal, mechanistic and epidemiological evaluations.

IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano et al., 2005; IARC, 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation

(Cogliano et al., 2005; IARC, 2006) concluded that formaldehyde causes NPC, based primarily on results from animal studies, with additional evidence from "the largest and most informative cohort study of industrial workers" (i.e., Hauptmann, et al., 2004). Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage tissues induced tumors at formaldehyde concentrations > 2 parts per million (ppm) as summarized by Nielsen et al. (2013) and later by Nielsen et al. (2017). This was considered consistent with formaldehyde's demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans" (IARC, 2006).

IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although the Working Group noted that it was a "small majority" who found the evidence to be sufficient. Neither Hauptmann et al. (2003) nor the subsequently updated study (Beane Freeman et al., 2009) published results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting aneuploidy in the blood of exposed workers (Zhang et al., 2010a), recently accepted for publication, provided supporting data, with the caveat that the study needed to be replicated (IARC, 2012). Indeed, proper replication of this study is still needed, because the study protocol was not consistent with adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH method (Zhang et al., 2005; Zhang et al., 2011) and other standards (American Society of Medical Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe and in many countries around the world protect workers from the levels of occupational formaldehyde exposures that were studied by Zhang et al. (2010a) in China making replication of the study logistically difficult. Proper replication of this study also will require use of methods to successfully distinguish between aneuploidy arising *in vivo* from aneuploidy that arises during the period of *in vitro* culture, as discussed in section 3.3.3 below.

Following the IARC review and classification, the National Toxicology Program (NTP) concluded in the 12th Report on Carcinogens (12th RoC) that formaldehyde causes nasopharyngeal cancer and myeloid leukemia (NTP, 2011) (Table 1). The 12th RoC stated "The most informative studies for evaluation of the risk of ML are the large cohort studies of industrial workers (the NCI, NIOSH, and

British cohorts) and the NCI nested case-control study¹ of lymphohematopoietic cancer in embalmers” and specifically that “Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships”. However, the NTP also noted “In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure” and that in the only case-control study examining ML (Blair et al., 2000) “an excess risk was found for chronic (but not acute) myeloid leukemia” (NTP, RoC, 12th edition, “Formaldehyde”, p.3).

2.1. Environmental Protection Agency integrated risk assessment program (IRIS)

Formaldehyde had been classified by the EPA as a “probable” human carcinogen (Group B1) in 1991 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1). The EPA (2010) also derived a draft inhalation unit risk (IUR) value of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu\text{g}/\text{m}^3$)² based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For rationale, the EPA said the classification “is supported by cohort analyses of embalmers, pathologists and anatomists (Hall et al., 1991; Hayes et al., 1990; Levine et al., 1984; Matanoski, 1989; Stroup et al., 1986; Walrath and Fraumeni, 1983, 1984)” despite the observation that “... SMR analyses of the large industrial cohorts do not indicate a similar association (Beane Freeman et al., 2009; Coggon et al., 2003; Pinkerton et al., 2004)” (EPA, 2010; page 4–180). The EPA also cited three meta-analyses (Bosetti et al., 2008; Collins and Lineker, 2004; Zhang et al., 2009) that largely included the same studies as providing additional evidence. Repeatedly reporting the same results, however, does not constitute independent or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers and embalmers studies and therefore, the meta-analyses, too, are redundant with the updated analyses of the NCI cohort workers and embalmers studies.

The conclusions in the Draft IRIS Assessment specific to myeloid leukemia are as follows:

“Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Hayes et al., 1990; Pinkerton et al., 2004; Stroup et al., 1986; Walrath and Fraumeni 1983, 1984; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia.” (EPA, 2010; pages 4–184, 4–185)

Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of funeral directors and embalmers (Hayes et al., 1990; Walrath and Fraumeni, 1983; 1984) these reports do not constitute independent evidence or consistency across studies.

¹ This study technically is not a “nested case-control study” but rather a pooled re-analysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not “nested” in any true cohort that could be accurately enumerated.

² This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride (4.4×10^{-6} per $\mu\text{g}/\text{m}^3$) (EPA, 2000; page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

Hauptmann et al. (2009) has been judged to have severe methodological flaws (Cole et al., 2010a; b). Separately, the Zhang et al. (2009) meta-analysis combined different exposure metrics (peak, average intensity, cumulative exposure, duration), and thus, the exposure metrics were not comparable across studies. A more methodologically rigorous approach would be to perform meta-analyses for similar exposure metrics, that is, a meta-RR for cumulative exposure, meta-RR for average exposure, meta-RR for duration of exposure (only one study reported results in relation to peak exposure, precluding a meta-analysis for peak exposure). As such, the Zhang et al. (2009) meta-analysis results are difficult to interpret and methodologically flawed. Finally, combining data in a meta-analyses does not overcome any systematic biases in the underlying studies (Greenland and Longnecker, 1992).

2.2. National academies peer-review process

The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review of the Draft IRIS Assessment. Following a series of meetings during the second half of 2010, the NRC issued the final peer-review report on April 8, 2011 (NRC, 2011) as a pre-publication copy. The Committee identified numerous constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in general (NRC, 2011). Though not directly charged to evaluate the Draft IRIS Assessment conclusions, the peer review raised important questions regarding the underlying methods giving rise to several conclusions, including the basic causal conclusions:

“EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—“all LHP cancers,” “all leukemias,” and “myeloid leukemias.” The committee does not support the grouping of “all LHP cancers” because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.” (NRC, 2011; page 11)

The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC, 2011). The absence of such a framework was judged by the committee as problematic:

“As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions.” (NRC, 2011; page 11)

The NRC peer review further pointed out that the EPA (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a).

In the 7th and final chapter of its review, entitled, “A Roadmap for Revision,” the NRC provided recommendations in two categories: “Critical Revisions of the Current Draft IRIS Assessment of

Formaldehyde,” and “Future Assessments and the IRIS Process” (NRC, 2011). NRC (2011) specifically identified the systematic review standards adopted by the Institute of Medicine (IOM), as being appropriate for such an analysis (IOM, 2011).

Following the release of the NRC (2011) peer review, Congress issued House Report No. 112–151 (US U.S. House, 2011), and directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) peer-review report into the IRIS process. In 2014, NRC released an additional report on the IRIS process (NRC, 2014a), and emphasized the importance of evidence integration for hazard identification, in which studies of higher quality and low risk of bias are given greater weight in drawing conclusions regarding causality.

As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three themes:

- Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment;
 - Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and
 - Epidemiological research examining the potential association between formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).
- (From: <https://www.epa.gov/iris/formaldehyde-workshop>)

A second workshop was announced at the meeting but never convened. Since then, the EPA submitted a progress report to Congress in 2015 (EPA, 2015) in response to a request from Congress (U.S. House, 2014, p. 59). Most recently, House Report No. 114–632 (U.S. House, 2016; page 57–59) and Senate Report No. 114–281 (U.S. Senate, 2016; page 62) have requested the allocation of funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that recommendations raised by the NRC (2011) were implemented.

3. New studies published since the 2011 NRC peer review of the draft IRIS assessment

Numerous studies and updated analyses have been published since the 2011 NRC peer review of the Draft IRIS Assessment, the findings of which, at least in part, fill many of the “data gaps” and address several key methodological issues highlighted in the NRC Committee recommendations (NRC, 2011). Below we summarize this new research, organized around the data streams (e.g., epidemiological, toxicological, and mode of action) for evidence integration and quantification of potential leukemia risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):

- **Epidemiological Evidence**
 - Discussion of the specific strengths, weaknesses and inconsistencies in several key studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. (p.113)
 - Clarification of the basis of the EPA’s interpretations of the Beane Freeman et al. (2009) results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (p.113)
 - Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (p. 113)
- **Toxicological Evidence**
 - Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA’s unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (p.110)

• Mode of Action Evidence

- Improving the understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (p. 58)
- Reconciliation of divergent statements regarding systemic delivery of formaldehyde, (p.59) as direct evidence of systemic delivery of formaldehyde is generally lacking. (p.5)
- Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (p. 5)

• Dose-Response Assessment

- Independent analyses of the dose-response models to confirm the degree to which the models fit the data appropriately. (p. 14)
- Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (p.14)
- Further justification of the selection and use of the NCI cohort (Beane Freeman et al., 2009) for calculation of unit risk because the cumulative exposure metric (used in the calculation of unit risk) was not related to leukemia risk in the NCI cohort. (p.112)

• Methods for Evidence Integration

- Development of an approach to weight of evidence that includes “a single integrative step after assessing all of the individual lines of evidence”. Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (p. 113)

A summary of each of these recommendations and data gaps, along with the new science that has been conducted to address them is provided in Table 2 and discussed in the following sections.

3.1. Epidemiological evidence

The NRC peer review called attention to the EPA’s sole reliance on epidemiological studies to determine causality, rather than integrating epidemiology data with the toxicological and mechanistic evidence. When inferring causation from epidemiology studies, the evidence is critically assessed and synthesized across a body of individual studies, with greater weight assigned to studies of higher quality (rather than assigning equal weight to each). Better epidemiological studies are those that implement individual level exposure data, and minimize the potential for systematic bias and confounding. The ascertainment of outcome and analysis using accurate (and specific) diagnosis are also critical in the causal evaluation. The NRC peer review noted that the grouping of “all LHPs” comprises 14 biologically distinct diagnoses in humans and should not be used in determinations of causality. There is some evidence that these diseases may originate from the same stem cell line (Gluzman et al., 2015; Goldstein, 2010) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.

After the NRC peer review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML. Only a few epidemiology studies considered AML specifically. Since the critical review (Checkoway et al., 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC peer review. The key strengths and limitations of these studies are highlighted below.

Table 2

Summary of NRC (2011) comments or identified data gaps and new formaldehyde science by lines of inquiry.

NRC (2011) Comment/Identified Data Gap	New Formaldehyde Science
A. Epidemiological Evidence	
Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (NRC, p. 113)	<ul style="list-style-type: none"> • New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. See: Checkoway et al., 2015 • Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. See: Checkoway et al., 2015 • A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoietic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation. See: Checkoway et al., 2012 • Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative ($p_{\text{trend}} = 0.05$) and peak ($p_{\text{trend}} = 0.003$) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. See: Checkoway et al., 2015 • Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941–2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure. See: Coggon et al., 2014 • Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. See: Meyers et al., 2013
Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (NRC, p. 113)	
Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (NRC, p. 112–113)	
The selection and use of the NCI cohort (Beane Freeman et al., 2009) should be further justified. (NRC, p. 112)	
B. Toxicological Evidence	
Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (NRC, p. 110)	<ul style="list-style-type: none"> • No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6-129F1-<i>Trp53</i>^{tm1Brd} mice. See: Morgan et al., 2017 • FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. See: Morgan et al., 2017
C. Mode of Action Evidence	
Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (NRC, p. 58)	<ul style="list-style-type: none"> • Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. See: Schroeter et al. (2014) • With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. See: Yu et al., 2015 • Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde). See: Lai et al., 2016; Pontel et al., 2015; Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; Lu et al., 2011 • Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically, not in the bone marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species – a probable prerequisite for leukemogenesis. See: Albertini and Kaden, 2016 • Reanalysis of selected raw data from the Zhang et al. (2010a) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect <i>in vivo</i> events, the reanalysis of the results provided by Zhang et al. (2010a) raise sufficient questions that limit the use of Zhang et al. (2010a) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. See: Gentry et al., 2013 • Additional analyses were performed on the study data obtained from the original study (Zhang et al., 2010a) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate haematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. See: Mundt et al., 2017
Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (NRC, p.5)	
Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (NRC, p. 5)	
D. Dose-Response Assessment	
Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (NRC, p. 14)	<ul style="list-style-type: none"> • The documentation of the methods applied in the Draft IRIS Assessment (EPA, 2010) lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the NCI cohort study (Beane Freeman et al., 2009). This

(continued on next page)

Table 2 (continued)

NRC (2011) Comment/Identified Data Gap	New Formaldehyde Science
BBDR models developed by Conolly and co-workers should be used. (p.58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (NRC, p.57)	lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. See: Van Landingham et al., 2016
Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (NASNRC, p.14)	<ul style="list-style-type: none"> • Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. <i>Work in progress</i>: Clewell et al., unpublished • Results of the “bottom-up” approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. See: Starr and Swenberg, 2013 • Updated “bottom-up” risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers. See: Starr and Swenberg, 2016
<p><i>E. Methods for Evidence Integration</i></p> <p>EPA’s approach to weight of evidence should include “a single integrative step after assessing all of the individual lines of evidence.” Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (NRC, p. 113)</p>	<ul style="list-style-type: none"> • A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. See: Rhomberg et al., 2011 • Additional frameworks have been developed to integrate evidence. See: Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2013; Rhomberg 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014. • Other agencies or advisory bodies have conducted assessments of the carcinogenicity of formaldehyde in a transparent manner. See: PAC, 2012; Bolt et al., 2016; Nielsen et al., 2017

3.1.1. Key studies and their strengths and limitations

Since the update of mortality in the US formaldehyde users and producers cohort (Beane Freeman et al., 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers (Meyers et al., 2013) and the UK industry-wide formaldehyde producers and users (Coggon et al., 2014). In addition, a large population registry-based case-control study of incident AML cases in the Nordic countries, a small occupational study in Italy and a large multicenter European study of occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published (Pira et al., 2014; Saberi Hosnijeh et al. 2013; Talibov et al., 2014).

3.1.1.1. NIOSH cohort study of garment workers. Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A total of 36 leukemia deaths was reported (SMR = 1.04, 95% CI 0.73–1.44, compared to US mortality rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML). Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a geometric standard deviation of 1.90 (Stayner et al., 1988). The formaldehyde resins used to treat permanent press fabrics had been reformulated over time, and as a result, the formaldehyde concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm estimated by NRC for years prior to 1970 (NRC, 2014b). Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67–2.05), noting that NIOSH investigators “continue to see limited evidence of an association between formaldehyde and leukemia” and that “the extended follow-up did not strengthen previously observed associations.” All 14 AML deaths occurred 20 or more years after first exposure to formaldehyde. The NIOSH study is a large cohort with adequate follow up but limited industrial hygiene measurements of historical formaldehyde

concentrations, as most workers were first exposed prior to 1970. Therefore, the study did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to various LHM including AML were performed using duration of exposure as a proxy for cumulative exposure. Information on smoking was also lacking.

3.1.1.2. Registry-based case control study of AML in Nordic countries. Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961 to 2005. The investigators matched 76,660 controls to cases by year of birth, sex, and country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81–0.97 for workers exposed to ≤ 0.171 ppm-years; HR 0.92, 95% CI 0.83–1.03 for workers exposed to 0.171–1.6 ppm-yr, and HR 1.17, 95% CI 0.91–1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde). The strengths of this study were its exposure assessment based on a validated JEM and the comprehensive ascertainment of incident AML cases (i.e., not deaths), resulting in high statistical power to detect increased risks, avoidance of survival bias, and the ability to consider and control for other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to cause leukemia. This study failed to find an association between benzene and AML; however, increased risk of AML may be limited to those with exposure to very high concentrations that historically occurred only in a few occupational settings, e.g., the rubber hydrochloride industry (Infante et al., 1977; Schnatter et al., 2012).

3.1.1.3. European prospective investigation into cancer and nutrition (EPIC) cohort study. Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and

metabolic risk factors. The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors among 477 incident leukemia cases (201 ML, including 113 AML, 237 lymphoid leukemia, and 39 other or unspecified leukemias) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh et al., 2013). Occupational exposures were estimated using a general population JEM that classified occupational codes of study subjects by categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the authors reported that work histories were missing on a large number of cohort members, and these individuals had to be excluded. Study investigators lacked detailed job histories (job tasks and duration) for others, and the resulting exposure misclassification would be expected to be non-differential, attenuating risk estimates. On the other hand, this is one of the few studies examining specific subtypes of leukemia with risk estimates adjusted for smoking and other risk factors. AML risk was not increased among the formaldehyde low-exposure group (HR 1.01, 95% CI 0.65–1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic lymphocytic leukemia of 1.45 (95% CI 0.46–4.56) was reported among those with high exposure to formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al., 2013).

3.1.1.4. UK formaldehyde users and producers cohort study. Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users and producers; however, the analysis grouped all ML and did not analyze AML mortality separately. Similar to other large industrial cohorts (Beane Freeman et al., 2009; Meyers et al., 2013), industrial hygiene measurements were not available in the early years and investigators estimated averages for job titles based on irritant symptoms and later measurements. Exposures were estimated to range from background (< 0.1 ppm), low exposure (0.1–0.5 ppm), moderate exposure (0.6–2.0 ppm) and high exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986) and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than the US cohort (approximately 4% of the cohort). Coggon et al., 2014 reported no increased mortality from ML (SMR 1.16, 95% CI 0.60–2.20 for background exposure; SMR 1.46, 95% CI 0.84–2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450–1.82 for high exposure). In a nested case-control analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was non-statistically significantly increased among workers exposed to high concentrations for < 1 year (OR 1.77, 95% CI 0.45–7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24–3.82) (Coggon et al., 2014).

3.1.1.5. Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia. Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to further investigate specific types of leukemias, including AML (which had never been reported for this cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6 of 13 CML deaths occurred among study subjects with less than one year of employment. For workers employed at least one year, the risk of AML was highest (but not statistically significant) among workers with peak exposures of ≥ 2.0 to < 4 ppm (HR 1.78, 95% CI

0.61–5.25) and no trend was seen with increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater, although the estimates were imprecise (HR 4.83, 95% CI 0.64–36.42 for peak exposure ≥ 2.0 to < 4 ppm based on 2 CML deaths and HR 5.32, 95% CI 0.81–34.90 for peak exposure ≥ 4 ppm based on 2 CML deaths).

3.1.2. Synthesis of epidemiology studies: exposure assessment issues identified by NRC

One of the major issues highlighted by the NRC peer review is that one exposure metric (peak exposure) was used to determine causality in the draft IRIS assessment, while a different exposure metric (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk.

The NRC (2011) review of the Draft IRIS Assessment stated “the reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action” [p.112]. NRC further elaborated:

“In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk.” (NRC, 2011, pp. 112–113)

The NRC recommended that the quality of exposure assessment relied upon in epidemiological evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence. Where known causal relationships have been observed, exposure-response relationships often are seen with various exposure metrics, with stronger associations seen when more relevant metrics and exposure time windows are examined. Results such as those reported by Beane Freeman et al. (2009) are a good example of conflicting findings: the conventional exposure metric, cumulative exposure, demonstrated no association with risk of ML, whereas a surrogate of ‘peak’ exposure suggested one (Beane Freeman et al., 2009). When evaluating differences between cumulative exposure and peak exposure, and comparing risks associated with these, several differences should be highlighted.

NCI investigators (Beane Freeman et al., 2009; Blair et al., 1986; Hauptmann et al., 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart et al., 1986). The authors reported a significant test for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to < 4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (> 0 to < 2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde (“There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure at the end of follow-up in 2004.” (Beane Freeman et al., 2009, p. 751). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps single) peak exposure. Hauptmann et al. (2003) acknowledged that “no measurements of peak exposure were available